PAX3

Common genetic pathways

Interspecific backcross analysis where *Pax3*$^{Sp-d}$ mice on a B6 background were crossed with Mus spretus showed several modifiers of hypopigmentation, craniofacial abnormalities, and viability. Belly spot size was modified by the agouti (or a closely linked) locus and an X-linked locus in *Pax3*$^{Sp-d}$ mice, as males show belly spotting more frequently (Asher et al., 1996a).

Two studies showed that PAX3 downregulation occurs when B16F10.9 melanoma cells transdifferentiate into a glial/schwann cell phenotype. Expression of the chimeric cytokine/receptor molecule Interleukin-6 receptor/interleukin-6 (IL6RIL6) acts on the transmembrane receptor gp130, which subsequently dimerizes and activates downstream signaling cascades. In the first study, **IL6RIL6 expression caused a decrease in PAX3 protein / mRNA levels in B16F10.9 melanoma cells**. This caused a decrease in *Mitf* mRNA, subsequent loss of melanogenesis, and transdifferentiation into a Schwann/glial cell phenotype. Phosphorylation of the transcription factor STAT3 on tyrosine 705 (Y705) was shown to be required for PAX3 downregulation by IL6RIL6, as a STAT3 Y705F mutant abolished the IL6RIL6 effects (Kamaraju et al., 2002). In the second study, **overexpression of the transcriptional regulator C/EBP-d, which is induced by IL6RIL6, resulted in downregulation of PAX3 protein**, *Mitf* mRNA downregulation, and decreased tyrosinase activity (Kamaraju et al., 2004).

Maternal diabetes results in abnormally high levels of glucose transport to the developing embryo. Analysis of **mouse models of diabetes showed that excess glucose acts directly on embryonic tissue and specifically causes embryonic levels of PAX3 to be reduced. This increases p53-dependent apoptosis in the developing neural tube and can lead to neural tube defects**, similar to the neural tube apoptosis seen in Splotch embryos (Fine et al., 1999, Phelan et al., 1997). **Similar inhibition of *Pax3* was seen by increasing oxidative stress via antimycin A injection**, and the resulting neural tube defects could be blocked by increased intake of alpha-tocopherol (vitamin E). This suggests that increased glucose mediates its effects on PAX3 via increased production of oxygen free radicals (Chang et al., 2003).

PAX3 expression appears to be inhibited by the secreted protein melanoma inhibitory activity (MIA), a protein associated with tumor progression and highly expressed in malignant melanoma. Decreased MIA expression in cultured HMB2 melanoma cells results in increased PAX3 expression. MIA suppression resulted in increased MITF expression, decreased PIAS3 expression, and reappearance of pigmentation (Tatzel et al., 2005).

GFB1 signaling in skin inhibits PAX3 expression, and this regulation is modulated by UV radiation. In the presence of UV radiation, the secretion of TGFB1 by keratinocytes is downregulated by JNK/AP1 signaling. This repression of TGFB1 disables the induction of SMAD signaling in melanocytes. This SMAD signaling normally downregulates *PAX3* mRNA levels in melanocytes; however, upon UV-induced TGFB1 repression, SMAD repression of *PAX3* is removed so that *PAX3* expression is upregulated 3-6 hours after UV stimulation. Specifically, SMAD4, in complex with SKI, binds directly to the *PAX3* promoter. The p53 pathway interacts with this TGFB1/SMAD signaling cascade in two ways. First, p53 contributes to the repression of TGFB1 through regulation of AP1. Second, UV irradiation triggers a p53-mediated pathway in keratinocytes that induces POMC/MSH production, which subsequently activates the cAMP/CREB pathway in melanocytes. The cAMP/CREB pathway is required along with PAX3 activation to activate *MITF* transcription, (similar to SOX10's requirement of cAMP for activation of *MITF*) (Yang et al., 2008).